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# Air pollution and cardiovascular disease: *car sick*

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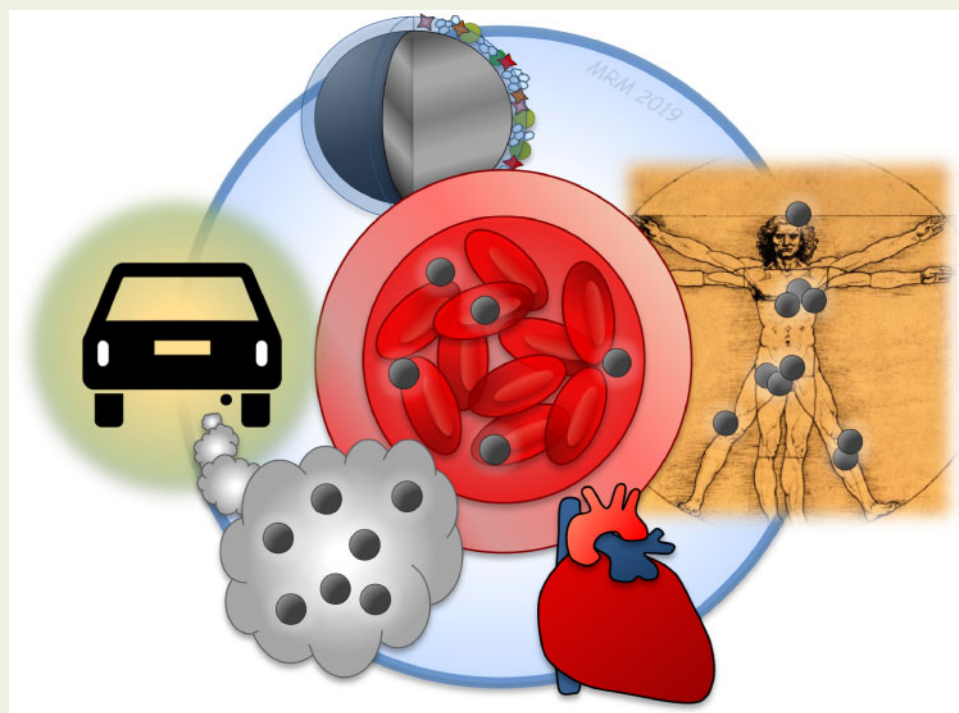
## Abstract

The cardiovascular effects of inhaled particle matter (PM) are responsible for a substantial morbidity and mortality attributed to air pollution. Ultrafine particles, like those in diesel exhaust emissions, are a major source of nanoparticles in urban environments, and it is these particles that have the capacity to induce the most significant health effects. Research has shown that diesel exhaust exposure can have many detrimental effects on the cardiovascular system both acutely and chronically. This review provides an overview of the cardiovascular effects on PM in air pollution, with an emphasis on ultrafine particles in vehicle exhaust. We consider the biological mechanisms underlying these cardiovascular effects of PM and postulate that cardiovascular dysfunction may be implicated in the effects of PM in other organ systems. The employment of multiple strategies to tackle air pollution, and especially ultrafine particles from vehicles, is likely to be accompanied by improvements in cardiovascular health.

## Keywords

Cardiovascular disease • Air pollution • Particulate matter • Translocation • Systemic effects

## Graphical Abstract



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# 1. Introduction

Public awareness of the health risks of air pollution has never been higher. Rarely is the subject out of the international media and its presence looms heavily over regulators and politicians. While we may have known for many centuries that air pollution is damaging to health, it is only in last two decades that the full magnitude of the problem has been recognized. The statistics are staggering. Air pollution is deemed to be responsible for several million premature deaths worldwide every single year.<sup>1,2</sup> Recent estimates based on further analysis of a modelled airborne particle concentration–effect curve have suggested that there may be up to 8.9 million excess deaths per year, specifically from outdoor air pollution.<sup>3</sup> Lifelong exposure to pollution is accompanied by a drastic shortening of life that varies, on average, from 3 to 6 months in modestly polluted countries such as the UK and USA, to 1–2 years from the notorious high pollution found in many areas of Sub-Saharan Africa and Asia.<sup>4</sup> Ambient (outdoor) air pollution is the 5th biggest risk factor for all-cause mortality, above more well-recognized risk factors such as low exercise and poor diet, and the number one environmental risk factor.<sup>5</sup> Indeed, it has been estimated that reducing air pollution to WHO air quality guidelines globally would increase life expectancy by 0.6 years; a benefit similar in magnitude to eradicating lung and breast cancer.<sup>4</sup> The morbidity accompanying air pollution is great (3.1% of global disability-adjusted life years), with phenomenal levels of associated economic cost (\$1–3 trillion US dollars, per year worldwide).<sup>2,6</sup> One of the reasons for these striking figures is that exposure to air pollution is near ubiquitous. It has been estimated that >90% of the world's population lives in areas of above World Health Organization (WHO) guidelines.<sup>7</sup> Levels of many air pollutants are on the rise in developing countries, but even in developed nations that have successfully lowered pollutants over the last 50 years, improvements have plateaued, and breeches of regulations in urban areas are common.

It has long been established that air pollution exacerbates respiratory conditions such as asthma and chronic pulmonary obstructive disease. Also, the once-surprising observation that air pollution is associated with cardiovascular disease is also now well-recognized in the 21st century. Nonetheless, the cardiovascular effects of pollution should not be dismissed. Cardiovascular conditions account for 40–60% of the premature mortality from air pollution.<sup>3,5,8</sup> Additionally, the multifaceted cardiovascular effects represent a substantial burden in their own right as well as through exacerbation of comorbidities. This review discusses the cardiovascular effects of air pollution, focusing on airborne particles and vehicle emissions as key pollutants of interest. The review is intended as an overview of the area (we direct the reader to the following for further detail<sup>9–14</sup>) with discussion of the potential role of the cardiovascular system in the actions of air pollution in other areas of the body.

# 2. Constituents of air pollution

There is a plethora of substances in the air that our body is exposed to and may need to protect against. These include both natural (e.g. forest fires, volcanic eruptions, aerosolized soil and dusts, pollen, and moulds) and anthropogenic (e.g. industry, power plants, traffic, household heating, cooking, construction, mechanical wear, agriculture, etc.) sources. Urban ambient air pollution has received the most attention due to the high density of urban populations, greater levels of traffic-derived emissions, and general increasing urbanization of societies worldwide.

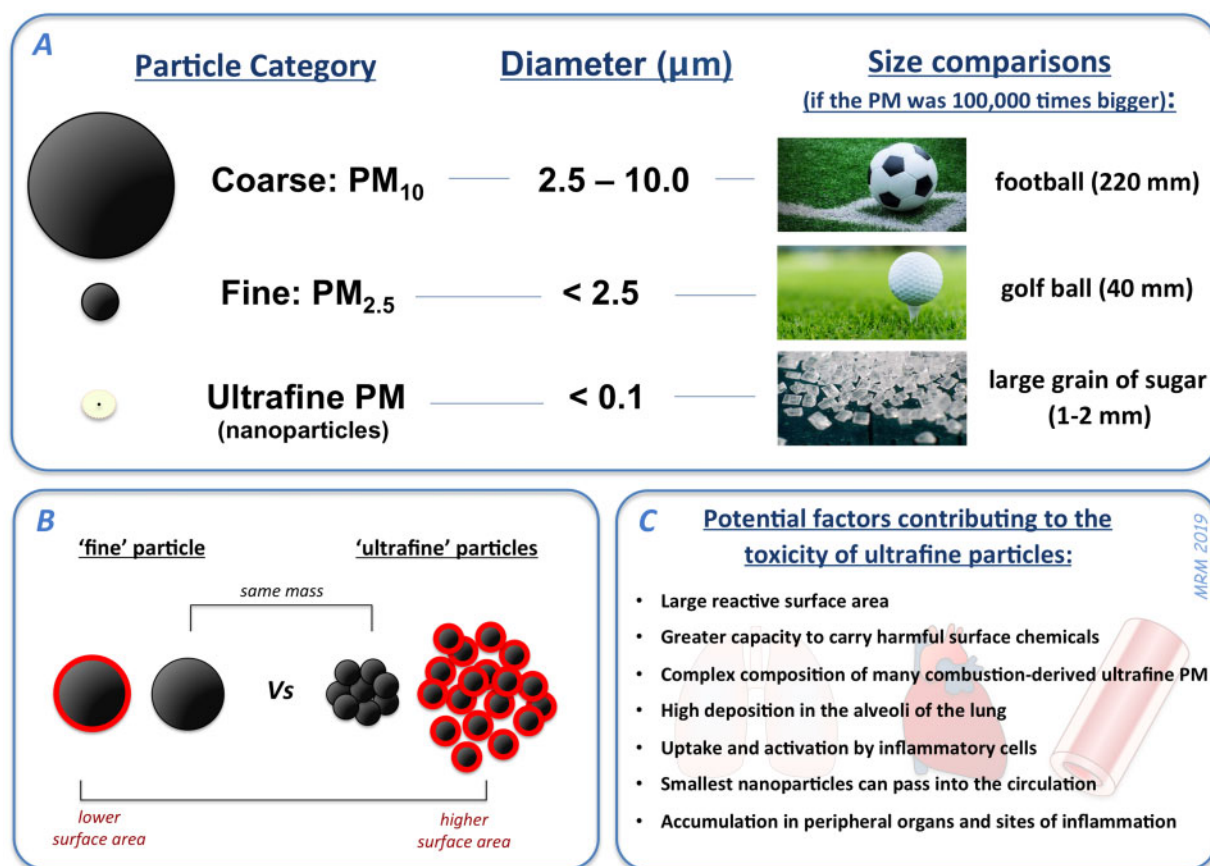
Urban pollution is a complex cocktail of chemicals that can also be broadly characterized into gases, semi-volatile liquids, and particles.<sup>15</sup> Numerous gases are found in urban air, such as sulphur dioxide (SO<sub>2</sub>), carbon dioxide (CO<sub>2</sub>) and monoxide (CO), ozone (O<sub>3</sub>), and nitrogen dioxide (NO<sub>2</sub>). Several gases in air pollution have oxidative properties, as well as other means to affect biological systems. Gaseous pollutants have the potential to cause short- and long-term health effects, possibly in an additive manner to particulates.<sup>9</sup> A diverse array of semi-volatile organic chemicals form the 'liquid' phase of air pollution, including methane, benzene, naphthalene, formaldehyde, polyaromatic hydrocarbons (PAHs), and alkanes. Semi-volatile chemicals associate or interact with gaseous and particulate phases of air pollutant. Consequently, distinguishing exposure to levels of individual pollutant constituents and isolating specific health effects can be challenging.

More consistent associations with health effects (and especially those of the cardiovascular system) tend to be found for particulate matter (PM) in the air. Environmental PM tends to be categorized, measured, and regulated in relation to particle size: coarse particles (PM<sub>10</sub>; particles with a diameter of 10 µm or less) and fine particles (PM<sub>2.5</sub>; diameter of 2.5 µm or less) (Figure 1). A third category, ultrafine particles (diameter of <100 nm, also termed 'nanoparticles'), is believed to be especially important for health, although it is not possible to measure ultrafine PM using monitoring networks in the environment at present. In general, the smaller size fractions exert greater effects due to their large reactive surface area and their ability to penetrate deep into the alveoli of the lungs and potentially into the bloodstream.<sup>12</sup>

Urban PM has a complex and varied composition. Elemental and organic carbon form a major part of combustion-derived PM, but non-carbon constituents such as various mineral dusts, sea salt, ammonium, nitrates, and sulfates are also present. Additionally, there is a vast array of chemical species present in urban PM, including organic carbon species (PAHs, nitro-PAHs, alkanes, alkenes, alkyl-benzenes, quinones, etc.) and redox-active transition metals. The availability of these chemicals on the surface of PM determines a significant proportion of the biological response to these particles once they are inhaled. Additionally, particles may accumulate small amounts of biological material, such as endotoxin, that are likely to play a role in airway inflammation and other aspects of the pathophysiological response. Particles in vehicle exhaust have been the subject of substantial research interest due to high proportion of ultrafine particles in these emissions (especially so for diesel exhaust; DE). The composition of combustion-derived nanoparticles, the high surface area to mass ratio of these smaller particles and their ability to penetrate deep in the body (see below) all suggest that these particles may induce a greater relative toxicity of these particles compared to other sources of PM.

# 3. Particulate matter and cardiovascular disease

In 1993, a landmark study in America looked at levels of air pollution in six difference major US cities over a 14–16-year period.<sup>16</sup> They found a clear relationship whereby higher levels of PM<sub>2.5</sub> were associated with hospital admissions and deaths from cardiovascular disease. Subsequently, epidemiological studies have shown clear associations between air pollution and various cardiovascular diseases including coronary artery disease,<sup>17–19</sup> cardiac arrhythmia and arrest,<sup>20–22</sup> heart



**Figure 1** Different size categories of PM in air pollution. (A)  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$  are routinely measured in the environment for monitoring and regulation of air pollution. Ultrafine PM (or nanoparticles: diameter <100 nm) comprise a proportion of urban  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$ , but due to the low mass of ultrafine PM it is not adequately accounted for by these larger PM metrics. (B) Ultrafine PM has a substantially higher surface area (red highlights) than an equivalent mass of fine PM. (C) The small size, and unique physicochemical properties, of ultrafine PM in urban environments/vehicle exhaust, engenders these particles with a higher potential to cause toxicity.

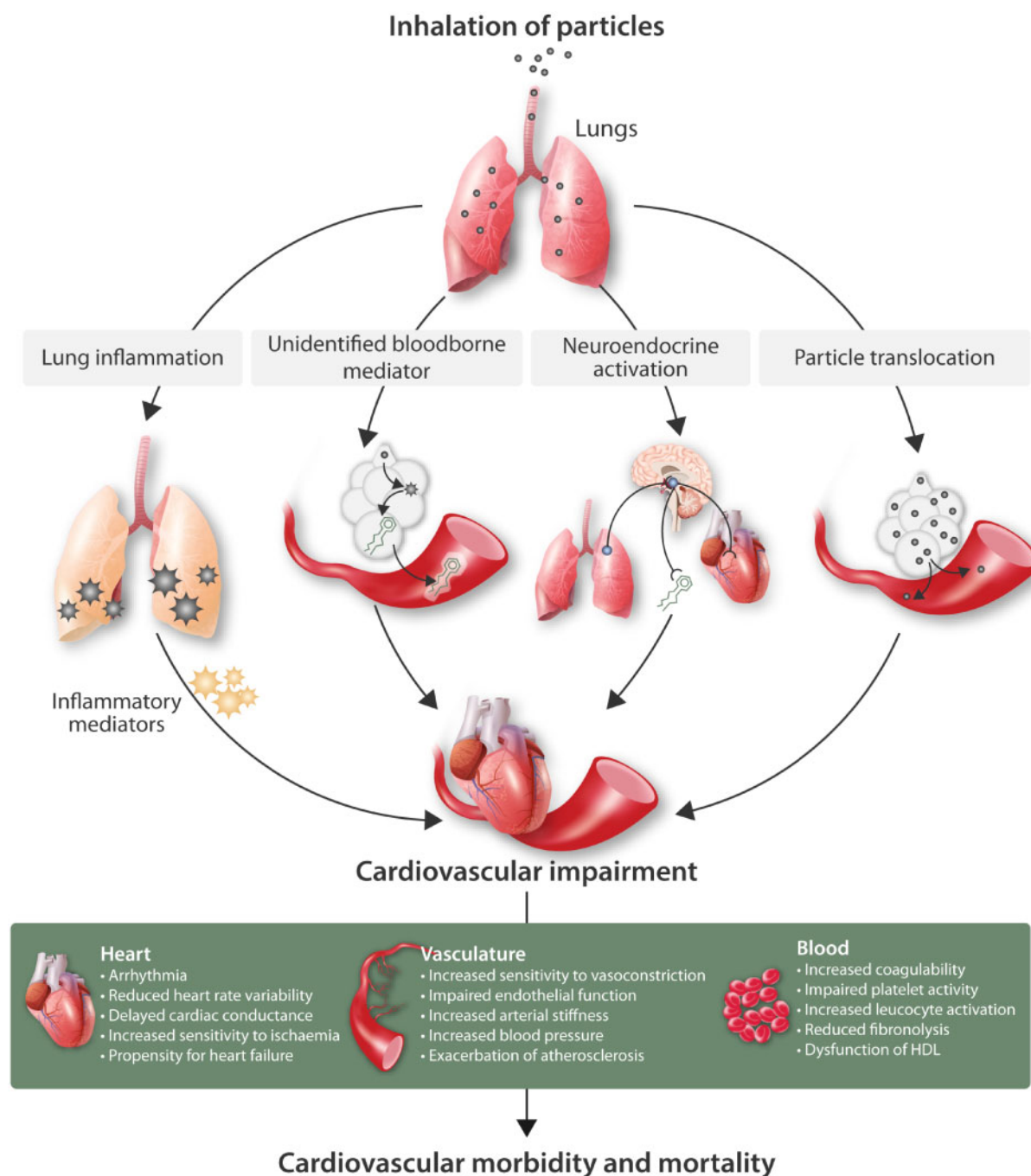
failure,<sup>23,24</sup> cerebrovascular disease,<sup>17,25–29</sup> peripheral arterial disease,<sup>30,31</sup> and venous thromboembolism<sup>32</sup> (see<sup>9</sup> for further details).

There is evidence that acute exposure is linked to cardiovascular events. Peters *et al.*<sup>33</sup> showed that individuals presenting with myocardial infarction were more likely to have been in traffic 1–2 h beforehand. Although accounting for confounding variables such as noise and stress is challenging, adjusting for level of exercise did not affect the association. Subsequent studies<sup>34</sup> have confirmed this association, and that it is independent of the form of transport used.<sup>35</sup>

Epidemiological studies have associated air pollution with a number of endpoints underpinning cardiovascular conditions (Figure 2). Exposure to urban air pollution is associated with atherosclerosis in a range of arterial beds.<sup>36–38</sup> While there is some inconsistency, PM exposure is also associated with a small (usually <5 mmHg for an inter-quartile increase in  $\text{PM}_{2.5}$ ), but significant elevation in blood pressure.<sup>39–42</sup> Elevated blood pressure will be partially determined by constriction or reduced vasodilatation of resistance vessels, which is evident after exposure to PM.<sup>43</sup> Exposure to  $\text{PM}_{2.5}$  and traffic (e.g. distance of residential address from a major road) is also linked to increased arterial stiffness,<sup>44–46</sup> although not all studies have found significant associations.<sup>47,48</sup>

A number of studies have made use of the non-invasive techniques to measure heart rate variability (HRV).<sup>11,49</sup> There is an overall trend towards reduction in HRV parameters. Although there is a large degree of inconsistency between parameters and studies,<sup>49,50</sup> the HRV effects associated with PM would be predictive of a worse prognosis at a population level. The relative ease of measuring HRV has been exploited in smaller panel studies where it is possible to measure personal exposure to pollutants (measured by portable devices, instead of estimates of pollution based on the nearest stationary monitor). In general, there is a trend towards detrimental HRV changes with PM exposure.<sup>51–55</sup> Use of a facemask to lower exposure to particulate air pollution can attenuate these changes in HRV.<sup>56–58</sup> The findings from epidemiological studies, results from animal studies (see below), and preventative effects of beta-blocker therapy,<sup>55,59</sup> suggest that PM alters cardiac rhythm through imbalance of the autonomic nervous system to decrease the vagal tone and increased sympathetic tone.<sup>60</sup> PM exposure also exacerbates cardiac ischaemia, as demonstrated by ST segment depression.<sup>9,61</sup> Beyond HRV,  $\text{PM}_{2.5}$  has been linked with an increase in the incidence of arrhythmia.<sup>62</sup> The nature of arrhythmia depends on the source of pollution, although anthropogenic sources were primarily responsible.





**Figure 2** Biological mechanisms linking inhaled particles to cardiovascular morbidity and mortality. Several hypotheses have been proposed for the means by which inhaled particles have actions on the cardiovascular system. These include: the passage of biological mediators (e.g. not only inflammatory mediators but also unidentified mediators that are not traditional cytokines) from the lung into the circulation; activation of alveoli sensory receptors leading to triggering of neural afferents which can alter the activity of the autonomic nervous system or release of endocrine molecules; direct passage of particles (or chemicals eluting from particles) into the circulation to directly impair cardiovascular function. We emphasize that there is considerable interplay between the four pathways shown, with inflammation and oxidative stress, in particular, having the capacity to amplify different stages of each pathways. The diagram also highlights that urban PM exerts many pathophysiological changes on different aspects of the cardiovascular system that ultimately increases cardiovascular morbidity and mortality.

PM exposure is linked to prothrombotic pathways.<sup>63</sup> While there are inconsistencies between studies looking at markers coagulation pathways,<sup>64–68</sup> this may reflect differences in experimental protocol

and variability in the extent of systemic inflammation occurring simultaneous (see below). Overall, there is a tendency for PM to increase blood fibrinogen, thrombin, von Willebrand factor and platelet

activity, and decrease *ex vivo* coagulation times.<sup>63</sup> Fibrinolysis is also blunted by PM, with decreases in t-PA release and up-regulation of PAI-1 pathways.<sup>63,69</sup>

Epidemiology studies have used blood and urine to look for mechanistic markers for the cardiovascular changes. PM or traffic exposure is associated with several biomarkers of oxidative stress, including oxidation of plasma proteins and lipids (e.g. malonaldehyde and protein 2-aminoadipic semialdehyde),<sup>70,71</sup> urinary isoprostanes,<sup>72</sup> and oxidative DNA adducts (e.g. 8-hydroxy-2'-deoxyguanosine).<sup>73–76</sup> In many cases, indications of oxidative stress coincide with markers of inflammation [e.g. C-reactive protein (CRP), tumour necrosis factor alpha (TNF- $\alpha$ ), various interleukins (IL)], although there is considerable variability in both.<sup>9,77</sup> Furthermore, DE particles induce a greater inflammatory response in individuals with genetic deficiencies in various antioxidant systems.<sup>78,79</sup> Recent work in healthy adults<sup>80</sup> has also expanded on data from animal studies<sup>81,82</sup> showing that PM<sub>2.5</sub> exposure is linked to impaired high-density lipoprotein function, leading to greater levels of circulating oxidized low-density lipoprotein (LDL); a key mediator in the early stages of atherosclerosis.

## 4. Controlled exposure studies in human subjects

Controlled exposure studies in healthy volunteers provide a unique opportunity to study specific pollutants in isolation or together, and with the potential to avoid or control many of the confounding variables of epidemiological studies. These studies have been essential in determining the mechanisms for the acute biological effects of air pollution in humans (Figure 2). The majority of studies investigate diesel exhaust (DE) using a 1 or 2 h exposure period, and a dose of DE 100–300  $\mu\text{g PM}/\text{m}^3$  to broadly model concentrations found from close proximity to exhaust emissions in heavy traffic, and representative of those reached in some international megacities.

Acute exposure to DE has prominent effects on the vasculature. Using forearm plethysmography, a 1 h exposure of DE impairs the ability of blood vessels to relax in response to infusions of vasodilator agents.<sup>83</sup> The pattern of inhibition between vasodilators suggested an impairment of endothelial function and the nitric oxide (NO) pathway.<sup>83,84</sup> DE also impairs endothelial responses in the skin microvasculature.<sup>85</sup> DE attenuated vascular responses rapidly (within 2 h) and, concerning, this impairment persisted for at least 24 h after the exposure.<sup>86</sup> DE exhaust can also decrease brachial artery diameter, but not flow-mediated vasodilation, in healthy subjects and those with metabolic syndrome, possibly through increases in circulating endothelin-1.<sup>87</sup> Others have found that, while DE increase vascular sensitivity to the endothelin pathway, these changes were more likely to be caused by decreased NO bioavailability rather than changes in ET-1 levels *per se*.<sup>88</sup> DE can also increase arterial stiffness<sup>89</sup> and raise systolic blood pressure,<sup>90</sup> both of which occurred within 0.5–2 h from the beginning of the exposure.

Controlled exposure to DE alters cardiac function. A notably greater depression was seen in the ST segment of the ECG in patients with ischaemic heart disease on exercise, indicating that DE worsened the cardiac ischaemic stress.<sup>91</sup> Acute exposures to DE tend not to be significantly associated with alterations in HRV parameters, suggesting that other constituents in urban air pollution are linked to effects on HRV that are observed in epidemiological studies.<sup>50</sup> Indeed, Devlin *et al.*<sup>92</sup> showed that controlled exposure to concentrated ambient particles (CAPs) caused changes in HRV and cardiac repolarization in elderly

individuals. A later study from the group showed that ultrafine CAPs had similar effects in patients with metabolic syndrome who were null for GSTM1 allele (a prominent antioxidant gene), but not a comparative group from the general population.<sup>93</sup> Likewise, Tong *et al.*<sup>94</sup> showed that CAPs affected HRV in healthy volunteers, which could be prevented by taking omega-3 fatty acid supplements.

Using a Badimon system (an *ex vivo* model of thrombosis using human blood flowing over a damaged blood vessel), our group demonstrated that acute exposure to DE promoted blood clotting, the mechanisms of which included activation of platelets (e.g. increased numbers of platelet-monocyte aggregates)<sup>95</sup> and reduced release of the fibrinolytic factor tissue-plasminogen activator (t-PA) from the vascular endothelium.<sup>83</sup> DE alters the expression of several antioxidant pathways in peripheral blood monocytes,<sup>96</sup> supporting a role for systemic oxidative stress in the cardiovascular actions of DE. While controlled exposure to DE does not appear to be associated with a consistent inflammatory response,<sup>97</sup> controlled exposures to CAPs increase blood plasminogen and markers of acute phase response in individuals with genetic deficiencies in various antioxidant systems.<sup>93</sup>

Two studies indicate that particles drive the acute cardiovascular effects of DE exposure. A retrofit 'particle trap' on the engine exhaust efficiently reduces particle mass in the DE and completely prevented the thrombotic actions of DE.<sup>98</sup> Filtering of particles from DE also prevented the vascular impairment observed with whole exhaust.<sup>99</sup> This observation was supported by a study<sup>100</sup> whereby volunteers were exposed to pure nitrogen dioxide at concentrations representative of whole exhaust; no acute cardiovascular effects were observed. Similarly, ozone exposure does not have acute cardiovascular effects,<sup>101</sup> although co-exposure of PM and ozone can cause vasoconstriction.<sup>102</sup>

Particle composition is important to cardiovascular effects of inhaled PM. Pure carbon particles (i.e. without any surface chemicals present on diesel exhaust particles) were not associated with cardiovascular effects.<sup>99</sup> Exposure to CAPs from rural environments can also increase blood pressure in comparison to that to that of filtered air,<sup>103</sup> whereas CAPs that largely consisted of salt (e.g. PM largely arising from maritime winds) had no effect.<sup>104</sup> Finally, both exhaust from idling engines and engines running in a 'city cycle' having detrimental cardiovascular effects.<sup>105</sup>

## 5. Mechanistic studies

There is a substantial body of work ranging from laboratory assays, cell cultures, isolated tissues, and *in vivo* studies in animals that build on findings in man to elucidate potential biological mechanisms for the cardiovascular effects of air pollution. This section provides a brief overview of this evidence and we refer readers to other reviews to broaden this narrative.<sup>9–13</sup>

Oxidative stress is a key biological mechanism by which diesel exhaust particles (DEP) exerts actions of the cardiovascular system.<sup>77</sup> In the absence of biological tissue, DEP has the capacity to generate superoxide free radicals,<sup>106</sup> and metals on the surface of DEP can assist in the production of hydroxyl free radicals via the Fenton reaction.<sup>107,108</sup> Once in contact with cells, DEP can also trigger oxidative stress via a number of different cellular mechanisms including NADPH oxidase, xanthine oxidase, uncoupling of NO synthase, and mitochondrial dysfunction.<sup>77,109</sup> The lung-lining fluid is rich in antioxidants that will presumably buffer the pro-oxidative actions of DEP, but particles can clearly overcome this defence to exert systemic oxidative actions.<sup>110</sup> Whether inhaled particles

can deplete antioxidant defences with high-dose or prolonged exposures, or if there are processes available by which particles can evade antioxidant defence, has yet to be fully established.

Inflammatory cells within the lung represent a defence mechanism for inhaled pollutants. Alveolar macrophages actively take up inhaled particles, as they would biological invaders. However, the physiochemical properties of combustion-derived PM promote activation of these cells<sup>111</sup> and sufficient doses of PM can induce inflammatory responses that cause local, and potentially systemic, inflammation. Cell culture studies demonstrate that while DEP has only modest direct effects on many cells (unless at very high concentrations), prior interaction with macrophages leads to a release of inflammatory mediators that can then induce marked inflammatory changes in other cells types including endothelial cells.<sup>112</sup> Oxidative stress and inflammation are likely to act synergistically to amplify each other's effects. For example, DEP can oxidatively modify lipids,<sup>82</sup> and that DEP and oxidized lipids together have synergistic actions of the expression profile of pathways linked to vascular inflammation.<sup>113</sup> Similarly, the ox-LDL receptor mediates a number of cardiovascular effects of vehicle exhaust emissions in atherosclerotic mice, including infiltration of monocytes and macrophages in the vessel wall.<sup>114</sup> While there is potential for inflammation to exacerbate the cardiovascular effects of inhaled particles in many different respects,<sup>115</sup> there is some doubt as to whether inflammation alone is the underlying cause of these effects.<sup>77</sup>

Experiments with isolated tissues have shown that DEP can directly induce endothelial dysfunction in the absence of inflammatory cells.<sup>43,106,116</sup> Pulmonary exposure to DEP in rodent models *in vivo* can induce vascular dysfunction with a similar profile of impairment to that seen with controlled exposure to DE in man, albeit depending on the model used and vascular bed studied.<sup>43</sup> As well as effects on the pulmonary and peripheral vasculature, animal models have shown that PM has detrimental effects on the coronary circulation.<sup>117–120</sup> PM<sub>2.5</sub> can also affect vascular smooth muscle phenotypes, and *in vivo* exposure increases the incidence of abdominal aortic aneurysm in angiotensin-II-infused atherosclerotic mice.<sup>121</sup>

Mouse models of atherosclerosis have been valuable for addressing the vascular effects of chronic exposure to PM.<sup>43</sup> Inhalation of PM promotes early events in atherogenesis, e.g. oxidation of LDL<sup>122</sup> and the adherence of leucocytes to the vascular wall.<sup>123</sup> Particles such as DEP increase the burden of atherosclerosis by a range of mechanisms including oxidative stress,<sup>81,82,113,124–129</sup> changes in arachidonic acid metabolites,<sup>82,114,130</sup> endothelin-1 pathways,<sup>131</sup> dysfunctional high-density lipoprotein (HDL),<sup>81,132</sup> endothelial nitric oxide synthase (eNOS) uncoupling,<sup>133</sup> and signalling through lectin-like oxidized LDL receptors.<sup>114,134</sup> Markers of plaque vulnerability are also increased by PM,<sup>126,128</sup> suggesting that urban PM and DEP exposure could trigger plaque rupture. Such observations would support those of epidemiological studies linking exposure to traffic with hospital admissions for acute myocardial infarction.

*In vivo* models have been used to look at the actions of PM on other facets of the cardiovascular system. Pulmonary exposure of DEP to rats potentiated the thrombotic occlusion of the carotid artery following arterial injury.<sup>135</sup> The response was more notable in response to DEP exposure compared to pure carbon nanoparticles or quartz particles, again emphasizing the importance of particle composition. Platelet activation and impaired fibrinolysis were important mechanisms,<sup>135</sup> complementing the findings of the clinical exposures to DE.<sup>83,95</sup> A range of thrombotic pathways could contribute to the prothrombotic effects of PM, including inflammation and oxidative stress,<sup>136–138</sup> tissue factor,<sup>139</sup>

fibrinogen binding,<sup>140</sup> impaired fibrinolysis,<sup>134,141</sup> and platelets<sup>142</sup> (reviewed by Robertson and Miller<sup>63</sup>).

Farraj *et al.* have performed detailed preclinical characterization of the cardiac effects of combustion-derived particles (see<sup>143</sup> for a review). As well as effects in healthy mice, the group have used isoproterenol-induced models of cardiomyopathy to show that inhalation of various types of PM promote arrhythmias, alterations in HRV and delays cardiac conduction.<sup>144–146</sup> Long-term exposure to PM promotes myocardial hypertrophy and loss of cardiac function.<sup>147</sup> Pulmonary exposure to DEP also induced arrhythmia and a greater degree of myocardial infarction in a rat model of myocardial infarction after coronary ligation.<sup>148</sup> Pharmacological inhibition of pulmonary sensory receptors or neural pathways diminished these effects, demonstrating a role for the neural systems in the cardiac effects of this air pollutant.<sup>148,149</sup> The renin-angiotensin system and oxidative stress have also been implicated in the cardiac effects of PM.<sup>150</sup> Direct exposure of cardiac myocytes to DEP can alter myocardial contractility and calcium handling,<sup>151</sup> suggesting that particle translocation (see below) may be a feasible mechanism accounting for the cardiac effects of inhaled PM.

## 6. From the lung to the cardiovascular system

The weight of mechanistic evidence provides confidence in the biological causality for epidemiological associations between PM and CVD. Both the initial pulmonary response to inhaled PM and the multifaceted nature of cardiovascular impairment have been well characterized. However, uncertainty in the biological processes that link inhalation of particles to that of the cardiovascular system still casts a shadow over the field. Three main theories have been proposed for the potential linking pathways<sup>152,153</sup> (Figure 2). The classical hypothesis is that inhaled pollutants activate inflammatory cells in the lung, leading to the release of inflammatory mediators that pass into the circulation to influence cardiovascular function.<sup>154</sup> There is a convincing case to link together lung inflammation and cardiovascular disease in general.<sup>155</sup> Also, markers of a systemic inflammation and oxidative stress are found in the blood after exposure to PM in blood humans and animal studies.<sup>9,156–158</sup> However, there is considerable inconsistency across different biomarkers and between studies, especially in human subjects, and the time-course of the inflammatory response often does not match other systemic effects. Nonetheless, there is a clear role for both inflammation and oxidative stress in multiple stages of the mode of action of inhaled PM<sup>77,152</sup> and these pathways represent a key means to amplify the signal from PM<sup>112</sup> even if they are not the critical underlying cause. A convincing argument has also been postulated for acute phase proteins (e.g. CRP or serum amyloid A) in mediating certain cardiovascular effects.<sup>159</sup> Finally, while conventional cytokines such as TNF- $\alpha$ , IL-6, and CRP do not seem to fully fit the bill, there is convincing evidence for an, as-yet, unidentified blood-borne mediator that could bring together the different stages of this pathway.<sup>160–162</sup>

The second theory is that inhaled pollutants activate alveolar receptors, stimulating sensory afferents that alter cardiovascular function via changes in autonomic balance or neuroendocrine regulation.<sup>143,163,164</sup> The pattern of HRV changes in response to PM would clearly indicate a shift in the balance of the autonomic nervous system towards reduced parasympathetic activity and increased sympathetic activity. There is strong evidence from animal studies showing that pharmacological inhibition of either alveolar sensory receptors or the beta-adrenergic receptors can attenuate the cardiac effects of DEP.<sup>148,149</sup> Chemical species

on the surface of DEP such as PAHs appear to be key in activating sensory afferents.<sup>165</sup> The role of this pathway on non-cardiac aspects of the cardiovascular system, such as the vasculature and blood, are less certain. However, the implication of the central nervous system (e.g. the hypothalamus–pituitary–adrenal axis) with subsequent endocrine release into the blood could fill this gap.<sup>164,166,167</sup>

The third hypothesis, termed ‘particle translocation’, is that the nanoparticle fraction of PM is small enough to cross over the lung epithelial barrier and enter the pulmonary circulation, whereby particles can then be carried in the blood directly to harm other areas of the cardiovascular system.<sup>168</sup> Proving this hypothesis is challenging given the technical limitations of visualizing these minute particles and detecting the very low levels of particles once they enter the systemic circulation. Studies in animals supported this possibility,<sup>169–172</sup> but evidence in man was limited. Recently our group used gold nanoparticles as a model to investigate this pathway.<sup>173,174</sup> Following 2 h inhalation of gold particles (5 nm primary size, median ~20 nm particles aggregates in aerosol) in healthy volunteers, gold could be detected in the blood within 15 min after the exposure, and by 24 h, all volunteers had measurable levels of gold in both their blood and urine. Gold was still present in blood and urine on recall of the volunteers 3 months later, indicating that these particles persist in the body and blood for very long periods of time. Subsequent studies in animals used a range of sizes of gold nanoparticles and showed that particles with primary size of <30 nm, but not larger particles, gained entry to the blood. Importantly, translocated gold in mice preferentially accumulated in atherosclerotic arteries compared to arteries without disease. Furthermore, inhaled gold reached areas of carotid vascular disease in patients with a history of stroke.<sup>173</sup> Recent studies by the laboratories of Calderon-Garciduenas and Maher<sup>175,176</sup> have used advanced electron microscopy techniques to identify iron-based particles in the brain and heart<sup>177</sup> of cadavers from heavily polluted Mexico City. The crystal structure and smooth-rounded surface suggests that these particles derive from combustion processes. While there are still some uncertainties as to whether these are inhaled particles, or that carbon-based particles also behave in the same way, these meticulous studies provide compelling evidence that exogenous particles can penetrate several organs of the body. Additionally, it is notable that the particles identified were associated with cellular damage, reinforcing the concept that particle translocation directly contributes to pathophysiological injury. Whether or not sufficient particle numbers translocate to induce cardiovascular effects is open for debate. However, the ability of DEP to generate free radicals, activate inflammatory cells, and directly impair vascular and cardiac function, suggests that should PM such as DEP also translocate in a similar manner to the gold nanoparticles, then these particles can promote cardiovascular disease.

## 7. Role of the cardiovascular system in the systemic effects of air pollution

In light of the many biological mechanisms by which PM can promote disease, it is logical that exposure will be associated with a range of extra-pulmonary effects.<sup>178</sup> Nonetheless, the diversity of these effects is somewhat alarming (Figure 3). These include exacerbation of metabolic syndrome and diabetes,<sup>42,179–181</sup> chronic kidney disease,<sup>182,183</sup> various cancers,<sup>184–187</sup> inflammatory bowel disease,<sup>188</sup> osteoporosis,<sup>189</sup> and liver

disease.<sup>190</sup> PM exposure alters circulating stem cell populations<sup>191,192</sup> and may promote rejection of organ transplants.<sup>193</sup> Air pollution has also been linked to skin diseases,<sup>194</sup> autoimmune diseases,<sup>195</sup> and infertility.<sup>196</sup>

Research into air pollution on the central nervous system has discovered links between air pollution and impaired cognition,<sup>197–199</sup> dementia<sup>200–202</sup> and even antisocial behaviour,<sup>203</sup> and teenage psychosis.<sup>204</sup> There is substantial attention on the early life effects of air pollution where maternal exposure has been linked to poor birth outcomes (e.g. preterm birth, low birth weight, stillbirth, or spontaneous abortion),<sup>205–207</sup> congenital defects,<sup>208</sup> and ill health of the children later in life.<sup>209</sup> Furthermore, early childhood exposure has been linked to effects on asthma,<sup>210</sup> lung development,<sup>211</sup> childhood leukaemia,<sup>212</sup> obesity,<sup>213</sup> attention disorders,<sup>214</sup> and autism.<sup>215</sup>

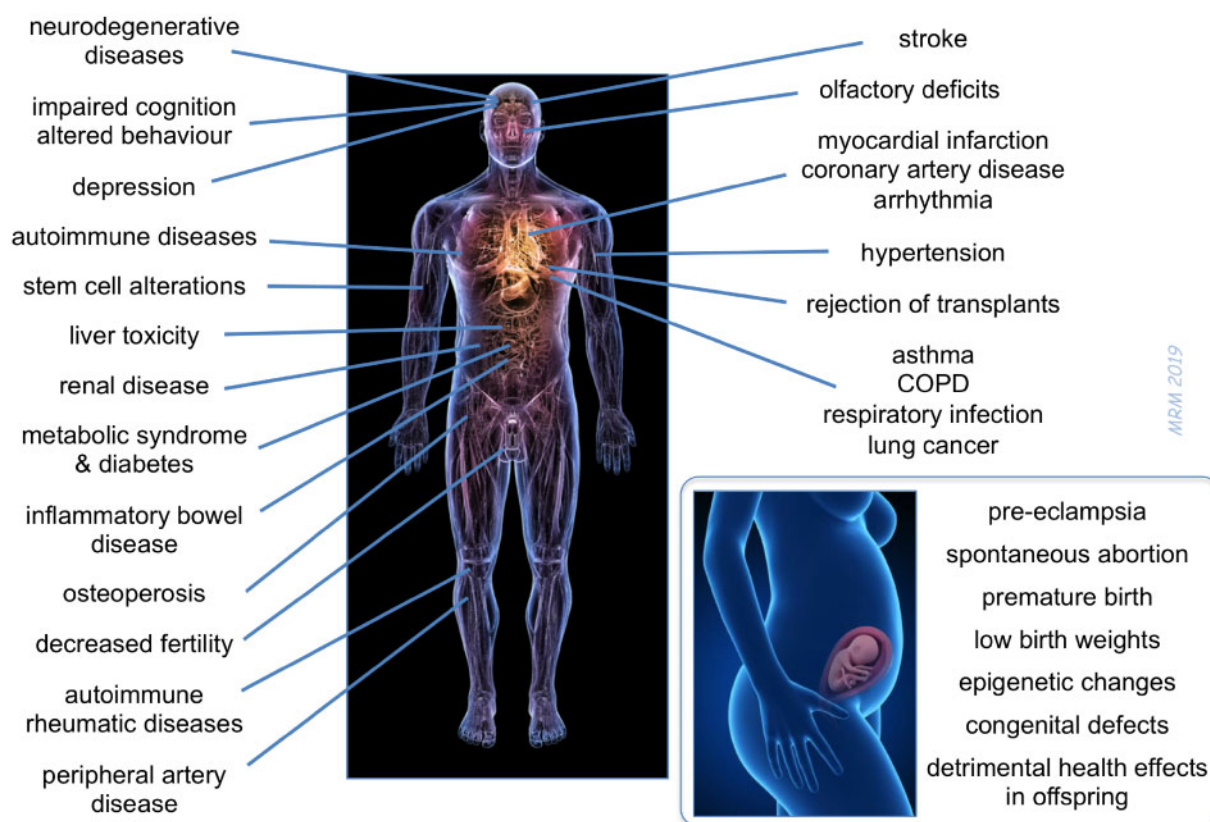
While the range of possible harmful effects of air pollution across the body is disturbing, our growing understanding of the mechanisms of air pollution goes some way to explaining these observations. Oxidative stress and inflammation are ubiquitous pathways in most diseases, and characteristically amplify each other’s molecular pathophysiology. While, the nature of the mechanism that ‘carries’ this ‘signal’ from the lung to other organs still requires elucidation, nanoparticle translocation, and neuroendocrine pathways could also bridge this gap. Additionally, several systemic effects of air pollution may be indirectly caused, or at least exacerbated, by the impairments in cardiovascular function caused by inhaled PM (Figure 4).

Widespread vascular dysfunction would be expected to be accompanied by raised blood pressure; a recognized risk factor for multiple morbidities beyond the cardiovascular system. Similarly, impaired circulatory control could result in inadequate perfusion of organs and potentially ischaemic damage when combined with an increased propensity for thromboembolism. In particular, the risk factors for diabetes are intricately linked to those of cardiovascular disease, with pathophysiology of the multiple vascular beds commonly developing with progression of Type 2 diabetes mellitus. Endothelial dysfunction usual precedes insulin resistance, and the dual vascular and proinflammatory effect of PM on both glucose homeostasis<sup>179</sup> and impairment of cardiovascular function will contribute to the co-morbidity. Indeed, animal studies show synergism between air pollution and hypercholesterolaemia, promoting insulin resistance, enlargement of fat beds, and inflammation of visceral adipose tissue, in addition to endothelial dysfunction<sup>180,181</sup> and development of atherosclerosis.<sup>216</sup>

Research into the effect of air pollution on the kidney is in its infancy. However, PM<sub>2.5</sub> has been linked to membranous nephropathy, decline in renal function and increased incidence of end-stage renal disease.<sup>183</sup> Many of the cardiovascular actions of PM could exacerbate the pathophysiology of kidney disease through elevated blood pressure, impaired renal perfusion, or inflammation. Indeed, administration of DEP to a rat model of adenine-induced chronic kidney disease decreased renal blood flow, in addition to increasing systemic blood pressure.<sup>182</sup> Work with different sized gold nanoparticles suggests that some particles be small enough to pass from the lung to the blood, but not be small enough to pass through the filtering mechanisms of the kidney.<sup>173</sup> Theoretically, accumulation of particles in the kidney would be expected to promote inflammation and oxidative stress and predispose other disease processes in the kidney.

It is reasonable to assume that the vascular effects of air pollution seen in many other areas of the body will be relevant to the brain. Given that approximately a third of stroke survivors would be expected to develop dementia within 5 years,<sup>217</sup> the established link between air pollution



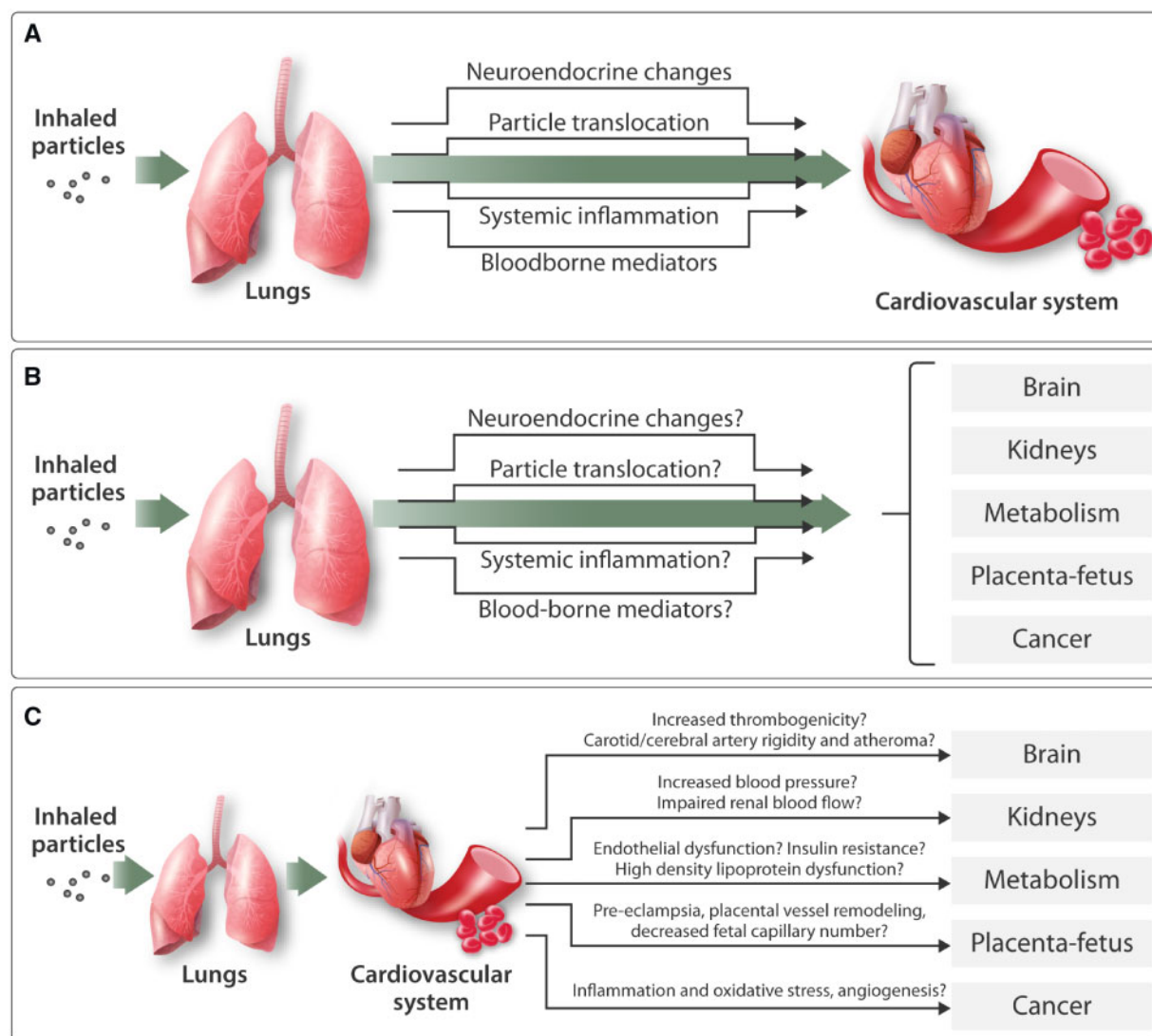


**Figure 3** Emerging evidence showing that air pollution has effects throughout the body. Over the last few decades it has become apparent that air pollution can effects beyond the pulmonary and cardiovascular system. This schematic highlights a number of examples of extrapulmonary effects of air pollution in general, although in most cases there is strong evidence for a role of particulates specifically. COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein.

(notably PM) and stroke<sup>26,29,218</sup> would also be expected to extend to cognitive impairment and dementias linked to circulatory causes. Atherosclerosis (both in the carotid and cerebral arteries), increased thrombogenicity and loss of vascular flexibility are plausible cardiovascular mechanisms by which PM could induce ischaemic and haemorrhagic stroke, respectively. In this regard, PM is associated with increases in carotid-intima thickness<sup>9,37,219</sup> and extensive carotid atheroma can have clinical manifestations linked to cerebral ischaemia or embolism. Increased endothelin-1<sup>220</sup> and angiotensin-II<sup>221</sup> concentrations are observed in the cerebral cortex in Alzheimer's disease, and build-up of these vasoconstrictors may contribute to the impairments in blood flow within the brain. Addressing the effects of PM on cerebral vasculature in man is more challenging, although Wellenius et al.<sup>222</sup> used transcranial Doppler ultrasound to look at non-structural changes in blood flow in the middle cerebral artery in elderly human subjects. An 8% increase in vascular resistance was observed per interquartile ( $3 \mu\text{g}/\text{m}^3$ ) increase in  $\text{PM}_{2.5}$ .<sup>222</sup> Polymorphisms in apolipoprotein E alleles are the most prevalent genetic risk factor for Alzheimer's disease, with carriers of the E4 allele experiencing accelerated cognitive decline and neurodegeneration.<sup>223</sup> However, apoE4 is also intrinsically linked to insulin resistance, microvascular integrity (including the blood-brain barrier) and atherosclerosis. Indeed ApoE4 is important in both the control of LDL-cholesterol in the blood and for clearance of amyloid-beta from the

brain, the accumulation of which is a hallmark of several forms of dementia. Thus it is interesting that carriers of the APOE4 allele also have greater susceptibility to the effects of air pollution than non-carriers, in terms of cognition<sup>224–226</sup> and indicators of metabolic syndrome.<sup>223,227</sup>

The effects of air pollution during pregnancy are a highly active area of research, and again there is a case for the cardiovascular effects of PM to play a role. Pre-eclampsia and other hypertensive disorders during pregnancy occur in ~10% of pregnancies. These conditions have a substantial health burden, potentially leading to seizures, long-term disabilities, and maternal or perinatal mortality.<sup>228</sup> The effects of exposure to air pollution on systemic blood pressure are relatively small and it is unclear whether such effect would have a significant contribution to pre-eclampsia. Nonetheless, research has suggested that in the region of 8% of hypertensive disorders during pregnancy we attributable to exposure to  $\text{PM}_{2.5}$  (based on  $>9 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  exposure throughout the entire pregnancy).<sup>229</sup> While a systemic endothelial dysfunction would be a likely mechanism by which PM could contribute to pre-eclampsia, PM exerts specific effects on the foetal-placental circulation. Exposure to ambient PM (close to roadside in Sao Paulo, Brazil) during pregnancy changes the structural integrity of the umbilical cord in mice.<sup>230</sup> Gestational exposure to diesel exhaust decreases placental blood flow and foetal capillary numbers in rabbits.<sup>231</sup> DE can also induce haemorrhage and compaction of the labyrinth vascular spaces in mice.<sup>232</sup>



**Figure 4** Biological mechanisms by which inhaled particles can impair the cardiovascular system and affect other organs in the body. (A) Several mechanisms have the potential to account for the ability of inhaled particles to induce cardiovascular actions: Inhaled particles stimulate sensory receptors in the lung, leading to changes in neural activity and endocrine release; small nanoparticles may pass ('translocate') into the circulation and directly act on the cardiovascular system; Induction of lung inflammation may result in a 'spill-over' of inflammatory mediators into the systemic circulation; other, as-yet unidentified, blood-borne mediators may drive the cardiovascular effects of inhaled particles. (B) The mechanisms proposed to account for the cardiovascular actions of inhaled particles could also be responsible for a range of effects in other organs of the body. (C) Various impairments in cardiovascular function could also indirectly contribute to the action of inhaled particles in other organs of the body.

Furthermore, an early report makes claims to have found suspect PM in the placenta of non-smoking mothers living in polluted areas<sup>233</sup> and there are some indications from rodent studies that blood-borne (non-environmental model) nanoparticles may reach the foetus.<sup>234,235</sup> It is also plausible that translocated particles could induce a localized inflammation and oxidative stress within the placenta, that induces chronic vascular remodelling and potentially increases in vascular permeability that could aid the passage of particles to the unborn child.

Finally, the vascular effects of certain pollutants may also play a role in tumour growth. The International Agency for Research on Cancer (IARC) classified diesel exhaust as a Class 1 carcinogen in 2012 based on the combined evidence from studies in miners, animal data, and the potential for DEP to cause genotoxicity *in vitro*.<sup>236</sup> However, while there is

a clear case for setting occupational exposure limits to diesel exhaust, extrapolation to risk for the general public is challenging.<sup>237</sup> Nonetheless, given the prevalence of diesel particles at roadsides (measured as elemental carbon) and lifetime exposure, researchers have postulated that this pollutant will contribute to the incidence of cancer in the general public.<sup>238</sup> Interestingly, a study by Xu *et al.*<sup>239</sup> investigated the influence of DEP on angiogenesis, with regard to the role that blood vessel formation plays in tumour formation. The investigators showed that inhalation of diesel exhaust led to increased growth of new blood vessels in hypoxic tissues in mice, while decreasing eNOS expression and increasing inflammatory cell penetration. It should be noted that the concentrations of DE used in the study were high (1 mg PM/m<sup>3</sup>) for a prolonged period to time (2–8 weeks). Furthermore, artificial *in vivo*

models of ischaemia were employed as a trigger for angiogenesis, whereas in other scenarios new blood vessel formation could be viewed as a beneficial response to improve blood supply to ischaemic regions. Therefore, while it remains to be established whether this process would contribute to the growth and development of tumours, the observations are intriguing nonetheless, and expand further on the growing list of cardiovascular effects of vehicle exhaust.

## 8. Conclusions and implications

The cardiovascular effects of ambient PM make an extensive contribution to the substantial burden of air pollution on health. Epidemiological studies have found sizeable (and largely consistent) associations between exposure to urban PM and cardiovascular mortality and morbidities, including myocardial infarction and stroke. Furthermore, exposure to PM has both acute (e.g. alterations in heart rate and increased blood pressure) and chronic (e.g. exacerbation of atherosclerosis) actions on the cardiovascular system. Pollutants such as diesel exhaust particles can exert a multitude of effects on different facets of the cardiovascular system. These include vascular dysfunction, increased susceptibility of the heart to ischaemic damage, and an increased propensity for thrombosis. An array of different biological pathways appears to underlie the cardiovascular actions of inhaled PM. Oxidative stress and inflammation remain key pathways by which inhaled PM may cause harm to the body, although the ability of these nanoparticle fractions of PM to translocate into the circulation could also account for the widespread effects of PM around the body. Translocation appears to be largely restricted to the smallest nanoparticles, and it is feasible that this could include a proportion of the particulates found in vehicle emissions such as diesel exhaust. Given the large reactive surface area of these particles, their recognized toxicity, and the potential harm from co-pollutants such as nitrogen dioxide, it is clear that reducing emissions from vehicles should be a priority for air quality strategies.

There are clear socioeconomic inequalities of air pollution exposure, both in terms of exposure to pollutants (low-cost housing is often in the areas of highest pollution) and associations with other risk factors for disease (deprivation is linked to poor diet, inactivity, and, often, greater levels of smoking, alcohol, and drug use). As well as the overlap and interactions between these risk factors, the impaired cardiovascular function associated with air pollution will further compound health. Raised blood pressure, propensity for thromboembolism, and cardiac inefficiency will, in themselves, be risk factors for co-morbidities. In addition to this, from a pathophysiological perspective, there are a number of means by which cardiovascular dysfunction linked to PM exposure may indirectly contribute to effect in other organ systems. These include links to cardiovascular complications of metabolic disease and diabetes, stroke and vascular dementia, changes to circulatory system of the placenta in pregnancy, and potentially vascularization of tumours. To what extent the cardiovascular system contributes to these conditions remains to be determined. However, these possibilities further emphasize the widespread effects of air pollution throughout the body. Practically, they also suggest that interventions that reduce air pollution could lead to beneficial effects on multiple organ systems.

While significant improvements in air quality have been made in many countries, air pollution is increasing beyond the already extreme levels frequently found in many developing nations. Furthermore, there are clear differences in guidelines for different limit levels of pollutants in different nations (e.g. WHO recommended annual  $PM_{2.5}$ :  $<10 \mu g/m^3$ ; USA:

$<12 \mu g/m^3$ ; Europe:  $<25 \mu g/m^3$ ; and China:  $<35 \mu g/m^3$ ). Furthermore, based on the current data available, there is no recognized level of air pollution that is considered 'safe'. Certainly, robust studies have shown that levels of PM and air pollution below stringent guidelines (e.g. WHO,  $PM_{2.5} <10 \mu g/m^3$ ) are still associated with significant health effects.<sup>129,240</sup> It is clear that air pollution is global concern that should not be met with complacency.

A combination of strategies should be used to reduce air pollution effectively. Indeed, a recent examination of the potential interventions in the UK has identified a number of strategies by which different sectors can tackle air pollution.<sup>241</sup> However, the report emphasizes that a concerted implementation of measures is required to realize gains in air quality that are unlikely to be possible from isolated interventions. In terms of pollutants, from a cardiovascular perspective alone, reducing PM should be a priority. Epidemiological assessments of cities that have successfully decreased particulate air pollution levels have reduced cardiovascular mortality.<sup>42</sup> Indeed, it is encouraging that a number of studies have shown that reduction of personal exposure to urban PM through use of facemasks has been accompanied by improvements in cardiovascular parameters.<sup>42,56–58,242</sup> Indoor air purifiers also appear to have beneficial effects in this regard, especially in cities with high levels of pollution.<sup>42,243</sup> The long-term consequences of these short-term benefits need to be established.

The mass metrics of  $PM_{10}$  and  $PM_{2.5}$  are not ideal for quantifying ultra-fine particles from vehicle exhaust.<sup>244</sup> Given the strong mechanistic evidence for the scale of harm that combustion-derived particles exert on the cardiovascular system, targeting PM from vehicle emissions may well be accompanied by improvements in cardiovascular health beyond that which would be estimated from reductions in  $PM_{10}$  and  $PM_{2.5}$ . Experimental studies in man have already shown that removal of particulates from diesel exhaust can prevent the acute cardiovascular parameters associated with this pollutant.<sup>98,99</sup> Rodent studies have also shown the potential for fuel additives that reduce particle numbers in tailpipe emissions to prevent the pro-atherosclerotic effects of DEP.<sup>245</sup> Modern combustion engines are substantially more efficient, with Euro 6 diesel engine emitting, on average,  $10\times$  less PM than a Euro 3 engine (albeit these are based on mass metrics from Euro emission standards for regulated diesel vehicles—emissions vary considerably with the type of vehicle and the situation is considerably more complicated and variable under real-world driving conditions).<sup>246</sup> Furthermore, the rapid rise in popularity of electric vehicle (and improvements in charging infrastructure, battery efficiency, and the electrification of commercial vehicles) suggests that the eradication of combustion-derived particles from vehicles may be achievable. And if this aspiration can be realized, significant improvements in cardiovascular health will likely follow.

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